REMARKS

Claims 1, 3-13, and 15-42 were previously pending with claims 7-12 and 19-24 withdrawn from consideration. By this paper claims 1, 4, 6, 13, 16, 18, 33, and 38 are amended and claims 7-12 and 19-24 are canceled without prejudice. The specification of the present application is also amended by this paper to include the chemical structure of the compound JTV-519. This chemical structure was disclosed in Kimura *et al.* (1999), the contents of which were incorporated by reference in the application as filed (see, for example, paragraphs 3 and 64 of the application as filed). Accordingly, no new matter is added by this amendment to the specification. Support for the amended claims is found in the application and claims as filed, and in the specification as hereby amended.

I. Claim Rejections Under 35 U.S.C. §112, 1st Paragraph

Claims 4, 5, 16, 17, 28, 29, 31, 32, 33-36 and 38-41 were rejected for allegedly failing to meet the enablement and written description requirements of 35 U.S.C. §112, 1st paragraph. In reply, Applicants respectfully traverse this rejection.

A. Written Description Requirement of 35 U.S.C. §112, 1st Paragraph

The Office Action alleges that the rejected claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Office Action also alleges that the specification fails to provide any structural features to adequately describe the genus of agents that may be administered. Applicants traverse this rejection. However, in order to expedite prosecution, but without conceding the correctness of the Examiner's position, Applicants have amended the claims to recite, *inter alia*, methods of treatment comprising administering an agent to a human subject wherein the agent is an N-substituted derivative of 1,4-benzothiazepine. The presently claimed invention is fully described by the specification.

Written description may be satisfied by disclosure of sufficiently detailed identifying characteristics such as complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between structure

and function, or some combination of such characteristics. Enzo Biochem, Inc. v. Gen-Probe, Inc. 323 F.3d 956, at 964 (Fed. Cir. 2002).

The specification of the present application states "in different embodiments, the agent is JTV-519 (also known as K-201) or any other compound in this class of compounds that are derivatives of 1,4-benzothiazepine (Yano et al., 2003; Kaneko, 1994, Hachida et al., 1999; Kimura et al., 1999)" (Emphasis added; See paragraph 64 of the application as filed). Thus, the specification provides explicit description of agents that are derivatives of 1,4-benzothiazepine. Applicants have amended the specification to explicitly disclose the chemical structure of JTV-519, which was originally incorporated by reference in Kimura *et al.* (1999) and Kaneko (1994). Accordingly, the specification also provides an explicit drawing of the chemical structure of JTV-519, from which it can be seen that JTV-519 is an N-substituted derivative of 1,4-benzothiazepine. Drawings alone may provide a written description of an invention as required by 35 U.S.C. §112 (Vas Cath, Inc. v. Mahurkar, 935 F.2d 1555, at 1662 (Fed. Cir. 1991). Accordingly, by disclosing the structure of JTV-519, the specification provides written description for compounds that are in the same class as JTV-519, i.e. compounds that, like JTV-519, are N-substituted derivatives of 1,4-benzothiazepine.

Furthermore, the specification discloses functional characteristics of the claimed agents. The specification states that an agent of the invention is one that "inhibits the dissociation of a FKBP12.6 binding protein from a type 2 ryanodine (RyR2) receptor" and that the agent may be "JTV-519 ...or any other compound in this class of compounds that are derivatives of 1,4, benzothiazepine." Thus, the specification discloses both the structural characteristics of the claimed agents and their function.

In view of the above remarks, Applicants request withdrawal of the rejection of the claims under 35 U.S.C. §112, 1st paragraph, for lack of written description.

B. Enablement Requirement of 35 U.S.C. §112, 1st Paragraph

The Office Action asserts that the specification "does not reasonably provide enablement for such a method of employing a genus of agents that inhibits dissociation of FKBP12.6 from RyR2 in a human subject." However, the Office Action states that the specification is "enabling for a

method of treating atrial tachyarrhythmia or inhibiting the onset of atrial tachyarrhythmia comprising administering to a subject a therapeutically effective amount of an agent that is disclosed in the specification or taught in the art" (emphasis added).

The presently claimed invention is directed to, *inter alia*, methods of treatment comprising administering an agent to a human subject wherein the agent is an N-substituted derivative of 1,4-benzothiazepine. As described above, the agents recited in the present claims are disclosed in the specification. Using the methods described in the specification and procedures known to those of ordinary skill in the art at the time of the invention, one of skill in the art could make other N-substituted 1,4,-benzothiazepine derivatives without undue experimentation. See, for example, paragraphs 87 to 89 of the application as filed, which describe, *inter alia*, suitable methods for synthesizing compounds. Similarly, using the description in the specification and methods known to those of ordinary skill in the art at the time of the invention, one of skill in the art could administer such N-substituted 1,4,-benzothiazepine derivatives to human subjects without undue experimentation. See, for example, paragraphs 55 to 60 of the application as filed, which teach, *inter alia*, pharmaceutically acceptable amounts, pharmaceutically acceptable carriers and suitable routes of administration. Accordingly, the presently claimed invention is enabled by the specification.

In view of the above remarks, Applicants request withdrawal of the rejection of the claims under 35 U.S.C. §112, 1st paragraph, for lack of enablement.

II. Claim Rejections Under 35 U.S.C. §103 (a)

Claims 1, 3-6, 13, 15-18, and 25-42 were rejected under 35 U.S.C. §103 (a) as allegedly being unpatentable in view of Nakaya *et al.* In reply, Applicants respectfully traverse this rejection.

The Office Action states that "Nakaya *et al.* teach inhibitory effects of a derivative of 1,4, benzothiazepine, JTV-519, in experimental atrial fibrillation in Langendorff-perfused guinea – pig hearts" and that although "Nakaya *et al.* do not explicitly teach treating a human subject... it would have been obvious to one having ordinary skill in the art at the time the invention was made to treat a human subject afflicted with atrial tachyarrhythmia by administering to the

human subject a therapeutically effective amount of JTV-519 with a reasonable expectation of success."

Applicants submit that Nakaya fails to teach or suggest a method for treating a human subject afflicted with atrial tachyarrhythmia comprising administering a therapeutically effective amount of a derivative of 1,4-benzothiazepine, and also fails to provide a reasonable expectation of success for such methods, for the reasons described below.

A. Nakaya *et al.* fail to show that 1,4-benzothiazepine derivatives are useful for the treatment of non-carbachol-induced atrial fibrillation *in vivo*.

Nakaya shows that the drug carbachol decreases the monophasic actual potential duration (MAP), decreases the effective refractory period (ERP), and decreases the atrial fibrillation threshold (AFT) in isolated guinea pig hearts stimulated by artificial electrical pacing, and that the addition of 1μM JTV-519 reverses the decrease in MAP duration and the decrease in ERP caused by carbachol. (See page 1367 and Figure 6 of Nakaya *et al.*). However, Nakaya fails to mention any effect of JTV-519 on AFT. Nakaya also shows that atrial fibrillation could be induced by carbachol in the presence of 0.3μM JTV-519 in 2 out of 5 isolated guinea pig hearts, but could not be induced by carbachol in six isolated guinea pig hearts in the presence of 1μM JTV-519.

Thus, at most, Nakaya demonstrates that JTV-519 may inhibit the induction of atrial fibrillation by provocation treatment using high doses of carbachol and electrical pacing in isolated hearts from guinea pigs. This falls far short of suggesting that JTV-519 is useful for treating physiologic atrial fibrillation *in vivo*, whether in guinea pigs, humans, or in other animals. The induction of atrial fibrillation by high doses of carbachol in combination with rapid electrical pacing represents an artificial *in vitro* model which is not representative of pathophysiologic AF mechanisms *in vivo*. In fact, Nakaya states that it was not possible to induce AF by electrical stimulation in the absence of carbachol. ("In the control condition AF could not be induced by a train of stimuli at an intensity up to 12 mA in Langendorff-perfused guinea-pig hearts").

One cannot conclude from Nakaya whether or not JTV-519 would inhibit AF in animals *in vivo*. In fact, the data presented in Nakaya further suggests that the effects of JTV-519 may be

insignificant for non-carbachol induced AF. Nakaya states that "[i]n the absence of any muscarinic agonist, JTV-519 at concentrations of 0.3 μM and 1μM insignificantly prolonged APD90" (page 1365, right column, first paragraph) and "JTV-519 insignificantly prolonged atrial action potential in the absence of $I_{K\,ACh}$ activation" (page 1367, left column, second paragraph).

Because Nakaya *et al.* fail to show that JTV-519 can be used to treat atrial fibrillation *in vivo*, Nakaya *et al.* provide no reasonable expectation that 1,4, benzothiazepine derivatives could successfully be used to treat pathophysiological (non-carbachol-induced) atrial fibrillation. This is in contrast to the present application where, in addition to showing that JTV-519 enables FKBP12.6 to bind to PKA-phosphorylated RyR2, the validity of the type 2 ryanodine receptor and (RyR2) and FKBP12.6 binding proteins as targets for antiarrhythmic drugs was confirmed in three different non-carbachol treated systems, namely in human heart tissue from patients undergoing cardiac transplantation (see paragraph 108 of published application), in a canine electrical pacing heart failure and arrhythmia model (see paragraph 108 of published application), and in a mouse exercised-induced arrhythmia model (see paragraph 176 of published application).

B. Nakaya *et al.* fail to teach or suggest that that 1,4, benzothiazepine derivatives are useful for the treatment of atrial fibrillation in humans.

Even if Nakaya *et al.* did suggest that JTV-519 could be used successfully to treat non-carbachol induced atrial fibrillation in guinea pigs *in vivo,* which it does not, it would still not be obvious from Nakaya *et al.* that JTV-519 could be used to treat atrial fibrillation in humans.

It has been demonstrated that animal tissues differ significantly from human tissues both in their electrophysiological characteristics relevant for arrhythmia mechanisms and their sensitivity to antiarrhythmic drugs. In a study by Wang *et al.* the efficacy of various antiarrhythmic drugs was tested in various different animal species (see Wang *et al.* (1990) Circulation 82; 274-283, a copy of which is submitted with this reply). Wang *et al.* found that "there are important species differences in the response to antiarrhythmic drugs" and that "although the responses were qualitatively similar in different species, quantitative differences in sensitivity and in the

magnitude of rate dependence make extrapolation to humans uncertain" (Wang *et al.* page 280, right column, paragraphs 2 and 3).

Furthermore, Wang *et al.* specifically found that the action of antiarrhythmic drugs in guinea pigs is not necessarily representative of their action in humans. Thus, Wang *et al.* stated "the response of canine atria were most similar to those of humans, and the response of guinea pigs tissue the least similar" (Wang *et al.* page 280, right column, paragraph 3), and "had our experiments been conducted only on guinea pig atria, we would have concluded that quinidine- and flecaindide-induced changes in atrial APD are not rate-dependent, a conclusion that would not apply to other species. Extrapolation from observations in other species to humans must therefore be very considered and requires confirmation either by direct observations in isolated human tissue samples or by evaluation of electrophysiological properties in the clinical electrophysiological laboratory" (Wang *et al.* page 281 last paragraph).

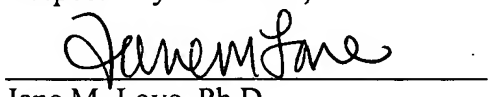
Because Nakaya *et al.* fail to provide data from animals other than guinea pigs, and provide no data from established large animal models of atrial fibrillation, Nakaya *et al.* provide no reasonable expectation that JTV-519 or other 1,4, benzothiazepine derivatives could successfully be used to treat atrial fibrillation in humans. This is in contrast to the present application where, in addition to showing that JTV-519 enables FKBP12.6 to bind to PKA-phosphorylated RyR2, the validity of the type 2 ryanodine receptor and (RyR2) and FKBP12.6 binding proteins as targets for antiarrhythmic drugs was confirmed in three different animal species, namely in humans, dogs, and mice.

Accordingly, in view of the above remarks, reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. §103 (a) is respectfully requested.

Conclusion

In view of the foregoing amendments and remarks, applicants believe that all of the Examiner's concerns have been addressed. Accordingly, applicants respectfully request reconsideration and allowance of the pending claims.

Respectfully submitted,



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Date: 12/6/06

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